PB90-240763

# Pesticide Fact Sheet Number 215: Folpet

(U.S.) Environmental Protection Agency, Washington, DC

25 Jun 87

U.S. Department of Commerce
National Technical Information Service
NTIS

| REPORT DOCUMENTATION PAGE | 1. REPORT NO. | 2. | 3. PB90-240763 |
|---|---|---|---|

| 4. Title and Subtitle | 5. Report Date |
|---|---|
| EPA Pesticide Fact Sheets - Folpet No. 215 | June 25, 1987 |
| | 6. |
| 7. Author(s) | 8. Performing Organization Rept. No. |
| EPA, Office of Pesticide Programs, Registration Division | 540/FS-90-094 |
| 9. Performing Organization Name and Address | 10. Project/Task/Work Unit No. |
| U.S. Environmental Protection Agency<br>Office of Pesticide Programs<br>Registration Division (H7505C)<br>401 M Street, SW<br>Washington, D.C. 20460 | 11. Contract(C) or Grant(G) No.<br>(C)<br>(G) |
| 12. Sponsoring Organization Name and Address | 13. Type of Report & Period Covered |
| Same as #9 | 14. |

15. Supplementary Notes

16. Abstract (Limit: 200 words)

This document contains up-to-date chemical information, including a summary of the Agency's regulatory position and rationale, on a specific pesticide or group of pesticides. A Fact Sheet is issued after one of the the following actions has occurred.

1. Issuance or reissuance of a registration standard,
2. Issuance of each special review document,
3. Registration of a significantly changed use pattern,
4. Registration of a new chemical, or
5. An immediate need for information to resolve controversial issues relating to a specific chemical or use pattern.

17. Document Analysis a. Descriptors

Pesticides, regulations, Chemical Information Fact Sheet, Use Patterns, science findings.

b. Identifiers/Open-Ended Terms

c. COSATI Field/Group

| 18. Availability Statement: | 19. Security Class (This Report) | 21. No. of Pages |
|---|---|---|
| Publicly Available | Unclassified | 14 |
| | 20. Security Class (This Page) Unclassified | 22. Price A03 |

United States
Environmental Protection
Agency

Office of Pesticides and Toxic Substances
Office of Pesticide Programs (TS-766C)
Washington, DC 20460

540/FS-90-094

EPA

# Pesticide Fact Sheet

PB90-240763

**Name of Chemical:** Folpet
**Reason for Issuance:** Registration Standard
**Date Issued:** June 25, 1987
**Fact Sheet Number:** 215

## 1. DESCRIPTION OF CHEMICAL

| | |
|---|---|
| Generic Name: | N-(trichloromethylthio) phthalimide |
| Common Names: | Folpet |
| Trade Names: | Folpan, Folpex, Phaltan and Thiophal |
| EPA Shaughnessy Code: | 081601 |
| Chemical Abstracts Service (CAS) Number: | 133-07-3 |
| Year of Initial Registration: | 1962 |
| Pesticide Type: | Fungicide |
| Chemical Family: | Dicarboximides or chlorinated Organosulfur compounds |
| U.S. Producer: | Chevron Chemical Company<br>Stauffer Chemical Company<br>Makteshim Beer Sheva Chemical Works, Ltd.<br>Calhio Chemicals, Inc. |

## 2. USE PATTERNS AND FORMULATIONS

Application sites: Terrestrial food crops, ornamental plants, in interior and exterior paints and coatings, and in plastics.

Types of formulations: Formulation intermediates containing 1.4% to 88% folpet, dusts containing 4% to 88% folpet, wettable powders containing 14.5% to 88% folpet, wettable

REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL
INFORMATION SERVICE
SPRINGFIELD, VA 22161

powder/dust containing 5% to 8.82% folpet, impregnated materials containing 0.0616% to 0.2288% folpet, flowable concentrates containing 13% and 44% folpet, liquid ready-to-use products containing 0.27% to 1.0% folpet, pressurized liquids containing 0.5% to 0.75% folpet, a pressurized dust containing 4.0% folpet and a 14.18% water soluble pellet (tablet).

Types and methods of application: Foliar spraying and dusting with hand, ground, and aerial equipment, dipping, drenching, brushing, rolling, padding, spraying and incorporating.

Usual carrier: Water, oil based paints and coatings, and vinyl plastics.

3. SCIENCE FINDINGS

Summary Science Statement: Folpet is classified as a Group B2 oncogen (probable human carcinogen); it causes developmental effects in laboratory animals; and it is a mutagen based on studies with bacteria and mouse lymphoma cells, and based on an *in vivo* *Drosophila* sex-linked recessive lethal assay. Folpet caused a dose-related oncogenic effect, adenocarcinomas of the duodenum, an uncommon tumor in mice. Technical folpet is a Category II pesticide based on reversible eye damage observed in studies with rabbits. Folpet is very highly toxic to fish and invertebrates. Available data are insufficient to assess the environmental fate of folpet. Plant and animal metabolism data and residue chemistry data are insufficient to support established tolerances for residues of folpet in or on 30 raw agricultural commodities.

Chemical characteristics:

| | |
|---|---|
| Physical state: | Crystalline solid |
| Color: | White |
| Melting point: | 177 °C |
| Boiling point: | 150 °C at 0.02 mm Hg |
| Solubility: | Insoluble in water, very low in aliphatic hydrocarbon solvents; low in aromatic polar, oxygenated and halocarbon solvents. |

| | |
|---|---|
| Vapor pressure: | No appreciable volatility at ordinary temperatures. |
| Stability: | Stable when stored in dry conditions at ambient or lower temperatures; not stable under alkaline conditions. |

Acute toxicological characteristics:

| | |
|---|---|
| Acute oral toxicity (rat): | Males - 43.8 g/kg<br>Females - 19.5 g/kg |
| Acute oral toxicity (mouse): | 2440 mg/kg |
| Acute dermal toxicity (rabbit): | > 5.0 g/kg |
| Acute inhalation toxicity (rat and mouse): | Inconclusive, inadequate to determine the acute inhalation toxicity. |
| Primary eye irritation (rabbit): | Reversible corneal opacity, prevented by immediately washing the exposed eye Folpet is a Toxicity Category II pesticide. |
| Primary dermal irritation (rabbit): | Not a skin irritant to rabbits |
| Dermal sensitization (guinea pig): | Sensitizer |

Chronic toxicological characteristics:

| | |
|---|---|
| 2-Gen. reproduction (rat): | Parental NOEL = 34.5 mg/kg/day |

Decreased weight gain in $F_1$ offspring. Reproductive NOEL in F2 matings was 800 ppm (40 mg/kg/day) based on decreased body weight gain, decreased fertility of males and a lowest effect level (LEL) of 3600 ppm (180 mg/kg/day).

| | |
|---|---|
| Subchronic feeding: | Rats - 90-Day feeding:<br>NOEL = 3000 ppm<br>LEL = 10,000 ppm<br>(Effects: decreased brain weight, total blood protein including albumin). |
| Chronic feeding/dosing Oncogenicity: | Mice - Oncogenicity:<br>Folpet was a positive carcinogen with a dose-related increased incidence of adenocarcinomas in the duodenum (a rare neoplasma in CD-1 mice in all dose groups (1,000, 5,000 and 12,000 ppm; or 142.9, 714.3 and 1714.2 mg/kg/day). |
| | Mice - Oncogenicity:<br>Folpet was a positive carcinogen with a dose-related statistically increased incidence of adenocarcinomas in the duodenum (a rare neoplasma in B6C3F1 mice) in all dose groups (1,000, 5,000 and 10,000 ppm; or 142.9, 714.3 1428.6 mg/kg/day). |
| | Rats - Sprague-Dawley rats fed a diet of 200, 800, and 3200 ppm folpet did not cause an oncogenic response. |
| | Dogs - 60 and 120 mg/kg/day caused non-significant reduction in mean body weight gains and decreased cholesterol, total protein, albumin and globulin. Lowest observed effect level (LOEL) was 60 mg/kg/day and the NOEL was 10 mg/kg/day. |
| Developmental effect: | Folpet was positive for developmental effects in both rabbits and rats. |
| | Rabbits - Developmental<br>NOEL = 10 mg/kg<br>Developmental LEL = 20 mg/kg<br>(hydrocephalus, domed skull, and irregularly shaped fontanelles) |

Rats - Developmental NOEL = 60 mg/kg. Developmental LEL = 360 mg/kg (possible incomplete ossification of one or both pubes and/or eschia).

Mutagenicity:

E. coli, WP 2 hcr, reverse mutation, positive direct-acting mutagen.

S. typhimurium, TA 1535, reverse mutation, positive direct-acting mutagen.

Mouse lymphoma cells - Positive in L5178Y/TK mouse lymphoma cells.

In vivo, Drosophila sex-linked recessive assay. Positive for sex-linked recessive lethals.

Dominant Lethal in mice - negative for mutations. Unscheduled DNA Synthesis - Positive in the presence of metabolic activation.

DNA Repair Assay - in B. subtilis and E. coli, Positive for DNA damage without metabolic activation.

Mitotic Recombination - Positive for recombinants, with or without metabolic activation in S. cerevisiae D3.

Mouse Somatic Cell Mutation Assay - negative for mutations. Significant pup mortality at all dose levels: NOEL for survival not established.

Metabolism:

In vitro stability in human blood - Half life of folpet in human blood is about 1 minute, degrades rapidly to phthalimide.

Physiological and Biochemical Behavioral Characteristics:

Foliar absorption: There are no data to characterize the absorption of folpet, its metabolites and degradates by roots and shoots of plants.

Translocation: There are no data to characterize the translocation of folpet, its metabolites and degradates in plants.

Mechanism of Pesticidal Action: Folpet inhibits normal cell division of a broad spectrum of microorganisms, however the precise mechanism of this effect is not understood.

Metabolism and Persistence in Plants and Animals: The metabolism and accumulation of folpet, its metabolites and degradates, are not understood.

Environmental Characteristics: Data gap.

Ecological Characteristics:

Hazards to Fish and Wildlife

| | |
|---|---|
| Bluegill sunfish | 96 hr $LC_{50}$ = 675 ppb |
| Rainbow trout | 96 hr $LC_{50}$ = 185 ppb |

Characterized as "highly toxic" to both coldwater and warmwater fish.

| | |
|---|---|
| <u>Daphnia magna</u>: | 48 hr $LC_{50}$ = 0.60 ppm Very highly toxic to aquatic invertebrates. |
| Avian Toxicity: | Slightly toxic:<br>$LC_{50}$ = Bobwhite quail > 2510 mg/kg<br>$LC_{50}$ = Mallard duck > 5000 ppm |
| Avian Reproduction: | Available data indicate that folpet does not impair avian reproduction. |

Potential problems related to endangered species:
Based on data on similar pesticides, the Agency is concerned about the effect of folpet exposure on endangered birds, fish, and insect species. The Agency will consult with the Office of Endangered Species regarding the potential of folpet use to jeopardize endangered species and may, pending the results of that consultation, require labeling restrictions to ensure protection of these species.

Efficacy Review Results: Folpet product registrations with EPA have been supported with efficacy data. Tolerant strains of target plant pathogens have not been reported.

Tolerance Assessments: List of Crops and Tolerances: The following table lists the present status for tolerances in parts per million (ppm) for residues of folpet:

| Raw Agricultural Commodity | Parts Per Million of Folpet Residues U.S. | Canada | Mexico | Codex |
|---|---|---|---|---|
| Apples | 25 | 25 | 25 | 10 |
| Avocados | 25 | 25 | 25 | - |
| Blackberries | 25 | 25 | - | - |
| Blueberries | 25 | 25 | - | 25 |
| Boysenberries | 25 | 25 | - | - |
| Celery | 50 | 30 | 50 | - |
| Cherries | 50 | 25 | - | 15 |
| Citrus Fruits | 15 | 15 | 15 | 10 |
| Crabapple | 25 | 25 | - | - |
| Cranberries | 25 | 25 | - | - |
| Cucumbers | 15 | 15 | 15 | 2 |
| Currants | 25 | 25 | - | - |
| Dewberries | 25 | 25 | - | - |
| Garlic | 15 | 15 | 15 | - |
| Gooseberries | 25 | 25 | - | - |
| Grapes | 25 | 25 | 25 | 25 |
| Huckleberries | 25 | 25 | - | - |
| Leeks | 50 | 25 | - | - |
| Lettuce | 50 | 25 | 50 | 15 |
| Loganberries | 25 | 25 | - | - |
| Melons | 15 | 15 | 15 | 2 |
| Onions (dry bulb) | 15 | 25 | 15 | 2 |
| Onions (green) | 50 | 25 | 50 | 2 |
| Pumpkins | 15 | 15 | - | - |
| Raspberries | 25 | 25 | - | 15 |
| Shallots | 50 | - | - | - |
| Squash (Summer) | 15 | 15 | 15 | - |
| Squash (Winter) | 15 | 15 | 15 | - |
| Strawberries | 25 | 25 | 25 | 20 |
| Tomatoes | 25 | 25 | 3 | 5 |

Results of tolerance assessment: Using the NOEL of 10 mg/kg/day from the chronic dog study and a 100 fold uncertainty factor to account for data gaps and the extrapolation of animal data to humans, the Provisional Acceptable Daily Intake (PADI) is 0.10 mg/kg/day. The Maximum Permissible Intake (MPI) for a 60 kg person is therefore 6.0 mg/day. Using this value existing tolerances utilize 123 % percent of the PADI based on nononcogenic effects. This calculation is conservative and is likely to decrease when based on actual residue data.

## 4. SUMMARY OF REGULATORY POSITIONS

- Folpet is a carcinogen in two strains of mice; however folpet was not carcinogenic in rats in a chronic feeding study. A second rat oncogenicity study is currently under review. Based on the oncogenicity data from studies with two strains of mice, mutagenicity data and structural similarity to captan, which is also an oncogen; the Agency has classified folpet as a B2 or probable human carcinogen.

  Based on a $Q_1^*$ of $3.49 \times 10^{-3}$ and estimated exposure levels from residues at tolerance levels (obtained under the "Food Factor" system), and assuming 100% of all foods have tolerance level residues, the cancer risk from dietary exposure to folpet is calculated as $3.1 \times 10^{-4}$. Due to the lack of folpet residue data, dietary risk estimates are based on 100% tolerance levels. When residue data required by the Registration Standard are received and reviewed, these risk estimates may be lower. Oncogenic risks from dermal exposure are not considered likely because folpet's half-life in blood is only 1 minute.

- Folpet causes developmental effects (toxicity) in rabbits and may be a potential human teratogenic pesticide. A teratology study with folpet in rabbits indicated developmental toxicity in the form of hydrocephalus and altered development of skull bones.

  The Agency calculated a dietary MOS of 90 (for females aged 13 and older) based on an acute single-day exposure to folpet as a result of consumption of food containing tolerance level residues, and the NOEL of 10 mg/kg/day for maternal and developmental toxicity. However, when the distribution of food consumption is considered, exposures for the upper 15 and 5 percent of the subpopulation yield MOS's of 50 and 33, respectively. When residue data required by the Registration Standard are received and reviewed, dietary MOS's are likely to be significantly higher.

  The Agency also calculated dermal MOS's for mixers/loaders/applicators on agricultural and home/garden sites. Based on the NOEL of 10 mg/kg/day for maternal and developmental toxicity, acute dermal exposures, and an estimated dermal absorption of 0.4%, MOS's for agricultural and home/garden sites are 340 and 47,000, respectively.

- Folpet is a mutagen in Salmonella, E. coli, mouse L5178Y/TK lymphoma cells and in the in vivo Drosophila sex-linked recessive lethal assay with metabolic activation. Folpet is positive in B. subtilis and E. coli DNA repair assays and in yeast for mitotic recombination. An in vitro study of chromosome aberration must be submitted.

- No new food uses will be registered until additional residue chemistry and chronic toxicology data are submitted and found to be acceptable for assessing the proposed use.

- Until product-specific data indicate otherwise, all folpet products must bear labeling with the signal word "WARNING" and the appropriate precautions for potential risk of hazard from eye exposure. Technical folpet caused corneal opacity that was present up to 7 days in a rabbit eye study.

- An interim 24 hour reentry interval is being imposed for agricultural crop uses of folpet until reentry data have been submitted, evaluated and found to support a different reentry interval. This reentry requirement reflects concern for the potential risk that may be associated with expected human exposure that could result from repeated entry into treated sites.

- The Agency is requiring the following studies to support all existing tolerances in agricultural commodities: plant and animal metabolism, storage stability, and analytical methodology. Metabolism of folpet in plants and animals has not been adequately defined. Plant and animal metabolites have not been quantified. No storage stability data are available for residues in plant and animal tissues.

- The Agency is requiring additional residue chemistry data for all established tolerances for folpet. Processing studies are required for tomato pomace, grape pomace, citrus fruit pulp and apple pomace. If animal metabolism data demostrate that detectable residues of concern may occur in animals from registered uses, then data quantitating the magnitude of the residue in animal tissues will be required to quantify human dietary exposure and for regulating the use of folpet to protect the public.

- While data gaps are being filled, currently registered folpet products may be sold, distributed, formulated and used in the United States. Registrants must provide or agree to develop additional data, as specified in the Data Appendix of the Folpet Registration Standard.

- The Agency is imposing precautionary labeling for all folpet products. The precautionary labeling requirements will provide information that will increase the awareness of users and promote proper use of folpet products.

- The Agency is requiring the use of certain protective clothing (long sleeve shirt and pants) and equipment (goggles or face shield) for all folpet products. The protective clothing and equipment requirements will reduce exposure to folpet products and decrease the risks associated with use of these products.

- The Agency is requiring labeling of all products to reflect the high toxicity of folpet to fish. Studies with rainbow trout and bluegill sunfish indicate that folpet is highly toxic to fish. The required labeling will warn users of the hazard of discharging folpet into lakes, streams, ponds, estuaries, oceans or public water.

- The Agency is requiring the use of a dust mask or similar protection against particle inhalation during mixing and loading of agricultural use and commercial ornamental plant use products and when reentering these treated sites within 24-hours after application to reduce the potential risk of hazards associated with the use of folpet products.

- The Agency is requiring the labels of industrial products to clearly state on the front panel "For Industrial Use Only", in order to avoid use of these products in non-industrial settings where workplace exposure is not well regulated.

Required Labeling:

Required labeling reflects use restrictions needed to reduce exposure to folpet. Submission of modified labeling addressing the following areas will be required within 90 days from the receipt of the Standard:

1. Ingredient Statements
2. Precautionary Statements
3. Environmental Hazards Statements
4. Use of Water from Treated Cranberry Bogs
5. Applicator Restriction for Greenhouse Uses
6. Use Precaution Statements
7. Reentry Interval
8. Signal Word Revision

5. SUMMARY OF MAJOR DATA GAPS

Product Chemistry

Toxicology:
- Acute Testing
- Subchronic Testing
- Chronic Testing
- Special Testing

Environmental Fate:
- Photodegradation
- Metabolism Studies - Laboratory
- Mobility Studies
- Dissipation Studies Field
- Accumulation Studies
- Subdivision K, Reentry Studies

Ecological Effects:
- Aquatic Organism Testing
- Nontarget Insect Testing - Aquatic Insects

Residue Chemistry:
- Metabolism in plants and livestock
- Residue analytical methods, for plant and animal residues
- Storage stablity data for raw agricultural commodities
- Magnitude of residues in food commodities

6. CONTACT PERSON AT EPA

Richard F. Mountfort
Product Manager (23)
Fungicide-Herbicide Branch
Registration Division (TS-767C)
Office of Pesticide Programs
Washington, DC 20460

B628
9



DISCLAIMER: The information presented in this Pesticide Fact Sheet is for informational purposes only and may not be used to fulfill data requirements for pesticide registration and reregistration.